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13. ABSTRACT (Maximum 200 Words) Chemical Intolerance (CI), including multiple chemical sensitivity, has been an intriguing problem in environmental health, and it has been suspected that CI played a role in Gulf War Syndrome. The uniqueness of the conference was its focus on neuro-biological changes, which has appeared to occur in individuals with CI. The conference provided a forum for the exchange of ideas among leading investigators in an effort to evaluate evidence regarding the role of neural plasticity in the development of CI. Among the topics discussed was a rationale for further research and clinical applications. Other disorders that overlap with CI, such as Gulf War Syndrome, chronic fatigue and fibromyalgia, were also be discussed. The conference was attended by toxicologists, basic neuroscientists, environmental health professionals and clinicians, including general practitioners and psychiatrists.				
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The Role of Neural Plasticity in Chemical Intolerance

A New York Academy of Sciences Conference

Introduction

Chemical intolerance (CI) is an exaggerated sensitivity to a class of inhalants that is different from allergy to protein allergens. Typically, volatile organic compounds which are odorous and toxic at higher levels cause problems for individuals with CI at levels much lower than those known to produce toxic effects. Individuals with CI report a wide variety of symptoms associated with chemical exposure, and assert that their condition is a result of prior exposure to chemicals (either short-term high-dose or long-term, lower-dose exposures). The most commonly reported symptoms include fatigue, depression, headaches, muscle and joint pain, irritability, memory and concentration difficulties, upper airway irritation, dizziness, anxiety, and gastrointestinal problems (1-5). The common feature of CI is reported in individuals experiencing symptoms as a result of various exposure settings, such as Gulf War veterans (Gulf War Syndrome), industrial workers, those living near hazardous waste sites, workers in so-called "sick buildings" and additional individuals of the general population in which exposure to new carpets, pesticides and other chemicals has occurred (1).

The Role of Neural Plasticity in Chemical Intolerance

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Body of Discussion

A. Development of Chemical Intolerance

The development of Chemical Intolerance (CI) has been described as a dual-phase process (1,6,7). The initiation phase is thought to be the stage during which either repeated exposure to chemicals, a high-level chemical exposure (such as that occurring during a chemical spill), or other stressful life events initiate the process of later sensitivity to chemicals. Thus, the initiation of CI appears to set the individual on a course during which very low levels of subsequent chemical exposure elicit the symptoms described above. The experience of symptoms is described as the elicitation phase; it is during this phase that individuals report extreme sensitivity to odors and feelings of illness from chemical exposures encountered at the home and workplace. Another term used for the elicitation phase is triggering (1). It is emphasized that while CI is typically thought to be initiated by repeated exposures to extremely low-level chemicals, this conception may be inaccurate. The initiation of CI may well be caused by low or moderate exposures (as in a remodeling event or pesticide spraying), or even high-level exposure (as in a chemical spill), while the elicitation of symptoms after subsequent encounter with chemicals appears to occur at much lower levels. Fiedler et al. (8) have reported that less than 40% of CI patients in their study could not identify an initiating event. Further, other events, such as previous life stressors, should be considered as possible initiators of CI (9-11).

To date, there are no clear clinical data which validate whether repeated chemical exposure causes the development of CI in a sensitive subpopulation. Although the prevalence of mild CI is 10-30% and severe CI is 4-6% in the U.S. population (10,12-14), there is much controversy regarding its acceptance as a true illness caused by prior chemical exposure. This doubt stems largely from: 1) the inability to rigorously identify true sensitivities to chemicals due to the unreliability of self-reports linking illness to chemical exposure, 2) the lack of blind challenges involving re-exposure to chemical during physiological/neuropsychological testing and 3) the diversity of symptoms and their overlap with other illness, such as somatoform disorder, chronic fatigue syndrome, fibromyalgia, panic disorder and posttraumatic stress disorder (PTSD) (2,8,13-25).

There exists increasing political, social and economic pressures to find a case definition for CI. The reason for the growing number of individuals with CI in the population is unknown. The increase may be attributed to an ever-increasing popularization of the belief that environmental

chemicals can produce CI. An alternative explanation is that the number of new chemicals in use grows each year, thereby initiating CI in increasing numbers of a sensitive population. Typically, those with CI complain of ill effects from chemicals that are present in very low concentrations in the environment, suggesting that an amplification has occurred in either the direct effects of chemicals or the perception of illness from chemicals.

B. Neural Sensitization Hypothesis of Chemical Intolerance

Neural sensitization is a common type of neural plasticity defined as the progressive and enduring enhancement in behavioral and neurochemical measures after repeated, intermittent exposure to a variety of stimuli, the most common of which are psychostimulants and environmental stressors. One of the leading working hypotheses to explain the amplification process for sensitivity to chemicals has been put forth by Bell and associates (7,26,27). They have noted that chemical sensitivity strongly resembles the phenomenon of sensitization in rodents observed after repeated exposure to psychostimulants or stress. They postulate that amplification of responses in chemically-sensitive individuals develops via a central nervous system (CNS) sensitization process, with particular emphasis on limbic system components due to their relatively high sensitivity to various perturbations and widespread involvement in neuroendocrine function, memory and cognitive functions. In the proposed workshop, the possibility that peripheral nervous system sensitization also contributes substantially to symptomatology of individuals with CI will be explored.

Several disciplines will be explored, each of which is expected to provide clues about the pathophysiology of CI in humans. Brief descriptions of each discipline and their expected contributions to further the understanding of the onset/amplification of symptoms are provided below.

1. Animal Models for CI: Role of Central Nervous System Plasticity:

Sensitization of behavioral and neurochemical responses to drugs of abuse and stress in rodents provides a potential framework for understanding how environmental chemicals may amplify a variety of biological/psychological responses after repeated, intermittent exposure. A direct test of this type of neural plasticity as a potential mechanism for CI indicates that repeated chemical exposure by relatively low concentrations of commonly-employed volatile organic compounds (formaldehyde, toluene) produces sensitization to dopaminergic agonists (28-32). Kindling is a subtype of sensitization in central pathways whereby repeated presentation of electrical stimuli to the brain that initially do not produce seizures can, with the passage of time, produce full-blown seizures in response to the same level of stimulus (33). Repeated chemical exposure has been shown to lower the threshold for kindling (34-37).

2. Neurogenic Inflammation: Chemical exposure can produce inflammation via sensory nerves located in the upper airways. Recently it has been recognized that some individuals can have an increased

inflammatory response to chemical irritants, which may be related to epidemics of other inflammatory responses, such as asthma and arthritis, in industrialized nations (38). It has recently been proposed that the site of inflammation mediated by stimulation of sensory nerve fibers in the upper airways may switch via access to the CNS, resulting in stimulation of other peripheral locations after subsequent chemical exposure (39). Studies of individuals reporting CI indicate increased damage to epithelial cells, potentially providing easy access to sensory neurons in the upper airway (22,40).

3. Neural Plasticity in Pathological Pain: Local inflammatory responses induced by tissue and/or nerve injury can produce pathological pain that persists for years in humans. In addition to peripheral neural mechanisms of sensitization, central neural plasticity has also been implicated in long-term responses to pain (41-43). Several studies indicate that pain perception is dependent upon past experience. Knowledge on the mechanisms of pathological pain, especially joint/muscle pain, which is prevalent in CI, may be pertinent to the development and/or maintenance of CI in humans. Local inflammatory responses involve a variety of neurotransmitters and cytokines (44-47), and evidence indicates that these modulate the hypothalamic-pituitary-adrenal (HPA) "stress" axis. In this fashion, local inflammation in the periphery may influence the state of the CNS circuitry via the HPA axis.

4. Cytokines: Effects on Chronic Fatigue States, Physiological Sleep and Sickness Behavior: Emerging evidence suggests the involvement of regulated cytokine production in fatigue states, physiological sleep and sickness behavior (48-52). Knowledge of normal biochemical cascades in the CNS producing sleep provides information on how abnormally enhanced fatigue states, such as exist in individuals with CI, may be mediated. Recent work indicates substantial overlap between individuals reporting CI and symptoms involved in chronic fatigue syndrome (2). In addition, cytokines interact with the HPA axis, which in turn can have profound effects on CNS plasticity (53,54).

5. Physiological Stress and the Neuroendocrine Axis: Regulation of the HPA axis may be critical in the polysymptomatology observed after chemical exposure in individuals with CI (55). Evidence suggests that early life stressors predispose individuals to a number of psychiatric disorders, and there is some evidence to suggest that stress may also be a risk factor in the development of CI (9-11).

6. Neural Conditioning: Several studies demonstrate the powerful ability of the CNS to modulate behavioral and neurochemical responses via conditioned stimuli (56-68). Olfactory stimuli (such as present in volatile organic compounds) may serve as strong conditioned cues to initiate symptoms in individuals with CI. Olfactory structures provide direct input to brain regions such as the amygdala, which has extensive connections to other limbic nuclei and is involved in emotion, memory and fear/avoidance responses. These responses may be especially relevant to CI since avoidance of chemicals is a hallmark of this disorder.

Conference: *Role of Neural Plasticity in Chemical Intolerance*

Conference Organizers: Drs. Barbara A. Sorg and Iris R. Bell

Background

Chemical intolerance (CI) is a term used to describe a feeling of illness from low levels of environmental chemicals and is sometimes used interchangeably with multiple chemical sensitivity, or MCS, because intolerance of chemicals is a hallmark of MCS. However, the term CI should be used to encompass a broader range of individuals who have been diagnosed with several other disorders, including:

- Multiple Chemical Sensitivity Syndrome (MCS)
- Gulf War Syndrome
- Chronic Fatigue Syndrome
- Fibromyalgia
- Solvent-exposed workers

Thus, CI is really a symptom in these illnesses. It is believed by some that this symptom may be indicative of neural pathways that are perturbed after repeated physiological (including chemical) and/or psychological stressors.

There are many disagreements as to the causes and very existence of these illnesses, especially regarding Gulf War Syndrome because of the variety of agents to which soldiers may have been exposed. Several previous conferences have been held to try to determine what the causes are for symptoms experienced in the above-listed illnesses. Many possibilities have been raised, but due to the wide variety of symptoms reported, there has not been a focal point on which to begin testing specific hypotheses.

Purpose of the Conference

The organizers of the conference believed that the best way to continue moving forward in determining the cause(s) for these illnesses was to find that focal point and essentially work backwards. Examination of several studies, primarily conducted in the United States, showed that neurological symptoms were the number one complaint among those reporting CI in different populations. Thus, these major symptom complaints were used as clues to the most obvious place to look for changes. Given the results collected so far, research efforts should move toward an understanding of the basic mechanisms underlying the neurobiological changes that may occur in CI.

It was therefore important to try to develop a series of testable hypotheses based upon the postulate that a change in nervous system function, or neural plasticity, plays a role in the development and/or maintenance of CI. To formulate these hypotheses, the organizers gathered together top scientists from other fields of basic neuroscience that potentially explain the debilitating symptoms. The major areas of focus at the conference were: 1) Chemical intolerance in humans; 2) Animal models for chemical intolerance and the role of neural plasticity; 3) Neural plasticity in pathological pain; 4) Cytokines, chronic fatigue states and

sickness behavior; 5) Physiological stress and the neuroendocrine axis; and 6) Neural conditioning.

Outcome of the Conference

Approximately 60 registrants attended the conference, which afforded a wonderful opportunity for many fruitful discussions, both during the conference and between sessions. Intriguing data were presented from all fields. One of the outcomes of the meeting was that researchers and clinicians whose work focused on the human conditions of Gulf War Illness, fibromyalgia, chronic fatigue syndrome, and MCS, were exposed to some of the basic biological processes involved in producing fatigue states, chronic pain, brain responses to physiological/psychological stress, and the fundamental neural circuitry changes underlying a form of memory called conditioning. Several of the basic scientists commented that this was an area of study of which they were previously unaware, and that it opened up new opportunities for application of their basic biological findings.

This conference was significant because it has moved the discussion beyond arguments over the authenticity of illnesses like Gulf War Syndrome and MCS. Although this conference may have done little to resolve the controversies, it has promoted a healthy dialogue regarding potential neurobiological substrates for this and related clinical syndromes.

Overall, the conference provided a forum for cross-talk between scientists and clinicians, and further, among subdisciplines in the neurosciences. These intriguing yet debilitating illnesses may begin to be approached in a logical and feasible manner if clinicians are provided with enough information to make it possible to consider treatment options. Neuroscientists in the various disciplines represented at this conference can provide some of this information but will need to expand efforts to offer more complete explanations for these illnesses.

THE COMPELLING ANOMALY OF CHEMICAL INTOLERANCE

Claudia S. Miller, M.D., M.S., University of Texas Health Science Center at San Antonio, San Antonio, Texas

In science, anomalies expose the limitations of existing paradigms and drive the search for new ones. In the late 1800's, physicians observed that certain illnesses spread from sick, feverish individuals to those contacting them, paving the way for the germ theory of disease. The germ theory served as a crude but elegant formulation that explained dozens of seemingly unrelated illnesses affecting literally every organ system. Today we are witnessing another medical anomaly—a unique pattern of illness involving chemically exposed groups in more than a dozen countries, who subsequently report multisystem symptoms and new-onset chemical, food and drug intolerances. These intolerances may be the hallmark for a new disease process, just as fever is a hallmark for infection. The fact that diverse demographic groups, groups sharing little in common save some initial chemical exposure event, develop these intolerances is a compelling anomaly pointing to a possible new theory of disease, one referred to as "Toxicant-induced Loss of Tolerance" or "TILT." TILT has the potential to explain a wide variety of illnesses, ranging from certain cases of asthma, migraine and depression to chronic fatigue, fibromyalgia, and "Gulf War Syndrome." It appears to evolve in two stages: (1) *Initiation*, characterized by a profound breakdown in prior, natural tolerance resulting from acute or chronic exposure to chemicals (pesticides, solvents, indoor air contaminants, etc.), followed by (2) *Triggering* of symptoms by small quantities of previously tolerated chemicals (traffic exhaust, fragrances, gasoline), foods, drugs, and food/drug combinations (alcohol, caffeine). The underlying dynamic remains an enigma. Observations that affected individuals respond to structurally unrelated drugs and experience cravings and withdrawal-like symptoms, paralleling drug addiction, suggest that multiple neurotransmitter pathways may be involved.

CONTROLLED EXPOSURES TO VOLATILE ORGANIC COMPOUNDS IN SENSITIVE SUBGROUPS

Nancy Fiedler, Ph.D., Howard M. Kipen, M.D., MPH University of Medicine and Dentistry of New Jersey - Robert Wood Johnson Medical School, Piscataway, New Jersey

Sensitivities to chemicals are characterized by symptoms in multiple organ systems in response to low level chemical exposures. This paper reviews studies of controlled exposures to odorants and to mixtures of volatile organic compounds. Sensitive subgroups include subjects who met Cullen (1987) criteria for multiple chemical sensitivity (MCS), Gulf war veterans with Chronic Fatigue Syndrome and chemical sensitivity (CFS/CS), and subjects with specific self-reported sensitivities (SRS) to methyl ter butyl ether (MTBE) in gasoline. All studies include comparison of age and sex-matched healthy controls. Studies of olfaction did not support unusual sensitivity, defined as lower odor thresholds, among MCS subjects; however, a dose-response pattern of symptoms was observed in response to suprathreshold concentrations of phenyl ethyl alcohol. In blinded, controlled exposures to clean air, gasoline, gasoline/11% MTBE, and gasoline/15% MTBE, a threshold effect was observed with SRS reporting significantly increased symptoms at gasoline/15% MTBE exposure. Autonomic arousal (heart & respiration rate; end-tidal CO₂) in response to odor of chemical mixtures may mediate symptoms for subjects with generalized chemical sensitivities but not for those whose sensitivities are confined to specific chemicals. For example, Gulf war veterans with CFS/CS experienced reduced end-tidal CO₂ when exposed to diesel fumes while exposure to MTBE did not produce any psychophysiologic changes in SRS. Controlled olfactory and exposure studies reveal that significant responses can be observed in chemically sensitive subjects even when de-adaptation has not occurred. However, these studies suggest that symptoms are not necessarily accompanied by changes in physiologic arousal. Subject characteristics play a critical role in outcomes.

NASAL CHEMOSENSITIVITY IN INDIVIDUALS REPORTING CHEMICAL INTOLERANCES

Kobal G. MD PhD, Dept. of Exp. Clin. Pharmacology, Univ. of Erlangen-Nuremberg, Germany

Having sophisticated olfactometric techniques available today we wanted test the hypothesis that in patients reporting chemical intolerances (CI) the sense of smell is affected. Twenty-three CI patients and as many control subjects participated in the experiments. Patients were selected based on their medical history according to the MCS criteria (Cullen 1987). The experiment consisted of two sessions that were separated by an interval of approximately 15 minutes. During this break patients were exposed to either 2-isopropyl alcohol (2-prop) at olfactory threshold level or room air. Acoustic rhinometry, a psychophysical olfactory test battery (odor identification, discrimination, threshold), and recording of chemosensory event-related potentials (trigeminal and olfactory) were performed before and after provocation. Acoustic rhinometry demonstrated that both groups exhibited a decreased mean volume of the anterior nasal cavity after provocation regardless of the type of challenge. CI patients tended to have a more pronounced decrease of nasal volume after provocation. Psychophysical investigations exhibited that controls performed better in the odor identification and odor discrimination test. In the threshold test there was a tendency of lower thresholds in controls. Olfactory event-related potential amplitudes PIN1 and N1P2 in controls were significantly larger after stimulation with H₂S regardless of the type of challenge. For the trigeminal system after stimulation with CO₂ amplitudes N1P2 but not PIN1 were larger in controls. In conclusion, the experiments revealed that CI patients do not seem to be more sensitive to odors at the afferent sensory level. Instead, they seem to be even less sensitive than controls. However, when further signal processing is involved at the cortical level, CI patients react differently to olfactory stimuli. Based on our data we hypothesize that CI patients have a decreased habituation to repeated stimuli and an altered evaluation of odors at the level of cognitive processes measurable by late components of event-related potential (e.g. P2 and P3). Also, the different way of mucosal swelling after provocation might indicate that neurogenic inflammation is involved in the pathophysiology of this phenomenon.

Black, D.W.: A nine-year follow-up of people diagnosed with multiple chemical sensitivities. Clinical symptoms and self-reported health status in persons reporting multiple chemical sensitivities (MCS) are presented from a 9-year follow-up study. Eighteen (69%) subjects from a sample of 26 persons originally studied in 1988 were followed up in 1997 and given structured interviews and self-report questionnaires. In terms of psychiatric diagnosis, 15 (83%) met DSM-IV criteria for a lifetime mood disorder, 10 (56%) for a lifetime anxiety disorder, and 10 (56%) for a lifetime somatoform disorder. None met criteria for a psychotic or substance use disorder. Seven (39%) of subjects met criteria for a personality disorder using the Personality Diagnostic Questionnaire-IV. Self-report data from the Illness Behavior Questionnaire and Symptom Checklist-90-Revised show little change from 1988. Subjects' physical complaints attributed to MCS were rank-ordered; the 10 most frequent were headaches, sore throat, joint pain, back pain, muscle tension or soreness, nausea, joint stiffness, eye inflammation, skin rash, and dry skin. Global assessment showed that 2 (11%) had "remitted," 8 (45%) were "much" or "very much" improved, 6 (33%) were "improved," and 2 (11%) were "unchanged/worse." Mean scores on the SF-36 health survey showed that compared to US population means, subjects reported worse physical functioning, more bodily pain, worse general health, worse social functioning, and more emotional-role impairment. Self-reported mental health was better than the US population mean. All subjects maintained a belief that they had MCS; 16 (89%) acknowledged that the diagnosis was controversial. The author concludes that the subjects remain strongly committed to their diagnosis of MCS. Most had improved since their original interview, but many remain symptomatic and continue to report ongoing lifestyle changes.

REPEATED FORMALDEHYDE EFFECTS IN AN ANIMAL MODEL FOR CHEMICAL INTOLERANCE

Barbara A. Sorg, Matthew L. Tschirgi, Samantha Swindell, Lichao Chen, and Jidong Fang, Washington State University, Pullman, Washington

Chemical intolerance is a phenomenon observed in multiple chemical sensitivity (MCS) syndrome, an ill-defined disorder in humans attributed to exposure to many volatile organic compounds. Amplification of symptoms in individuals with MCS resembles the phenomenon of psychostimulant and stress-induced sensitization in rodents. We have recently tested in rats the hypothesis that repeated chemical exposure produces sensitization of central nervous system (CNS) circuitry. A rat model of MCS in our laboratory has employed several endpoints of CNS function after repeated formaldehyde (Form) exposure (1 h/day x 5 days/wk x 4 wk). Repeated Form exposure produced behavioral sensitization to later cocaine injection, suggesting altered dopaminergic sensitivity in mesolimbic pathways. Rats given repeated Form also demonstrate increased fear conditioning to odor paired with footshock, implicating amplification of neural circuitry guiding fear responding to conditioned odor cues. Recent studies examining the effects of repeated Form on locomotor activity during daily exposures showed a decrease in rearing activity after 12-15 days of Form exposure compared to Air-exposed controls, implicating potential changes in fatigue or sleep states. EEG recordings taken 1 wk after withdrawal from daily Form indicate altered activity both basally and after subsequent challenge with Form odor (15 min challenge). Overall, these findings indicate that repeated low-level chemical exposure can produce behavioral changes akin to those observed in individuals with MCS, such as greater sensitivity to chemicals manifest as increased anxiety upon chemical exposure and possibly altered fatigue and/or sleep. Study of the underlying CNS changes will provide a basis for mechanistically-based animal models for MCS.

Does the kindling model of epilepsy contribute to our understanding of multiple chemical sensitivity? ME Gilbert, Neurotoxicology, NHEERL, US EPA, Research Triangle Park, NC.

Multiple chemical sensitivity (MCS) is a phenomenon whereby individuals report an increased sensitivity to low levels of chemicals in the environment. Kindling is a model of synaptic plasticity whereby repeated low level electrical stimulation to a number of brain sites leads to permanent increases in seizure susceptibility. Stimulation that is initially subthreshold for subclinical seizure provocation, comes over time, to elicit full blown motor seizures. Kindling can also be induced by chemical stimulation and repeated exposures to some pesticides have been shown to induce signs of behavioral seizure, facilitate subsequent electrical kindling, and induce subclinical electrographic signs of hyperexcitability in the amygdala. Many of the symptoms of MCS suggest that CNS limbic pathways involved in anxiety are altered in individuals reporting MCS. Limbic structures are among the most susceptible to kindling-induced seizures and persistent cognitive and emotional sequella have been associated with temporal lobe epilepsy (TLE) in humans and kindling in animals. Thus, a number of parallels exist between kindling and MCS phenomena, leading to initial speculations that MCS may occur via a kindling-like mechanism. However, kindling requires the activation of electrographic seizure discharge and has thus been primarily examined as a model for TLE. Events leading to the initial evocation of a subclinical electrographic seizure have been much less well studied. It is perhaps these events that may serve as a more appropriate model for the enhanced chemical responsiveness characteristic of MCS. Alternatively, kindling may be useful as a tool to selectively increase sensitivity in subcomponents of the neural fear circuit to address questions relating the role of anxiety in the development and expression of MCS.

A GENETIC RAT MODEL OF CHOLINERGIC HYPERSENSITIVITY: IMPLICATIONS FOR CHEMICAL INTOLERANCE, CHRONIC FATIGUE AND ASTHMA

David H. Overstreet, Ph.D. UNC Department of Psychiatry, Chapel Hill, North Carolina.

The fact that only some individuals exposed to environmental chemicals develop chemical intolerance raises the possibility that genetic factors could contribute. The present communication summarizes evidence from a genetic animal model of cholinergic hypersensitivity that suggests that an abnormal cholinergic system could be one predisposing genetic factor. The Flinders Sensitive Line (FSL) rats were established by selective breeding for increased responses to an organophosphate pesticide. It was subsequently found that these FSL rats were also more sensitive to directly muscarinic agonists and had elevated hippocampal and striatal muscarinic receptors compared to the selectively bred parallel group, the Flinders Resistant Line (FRL) rats, or randomly bred control rats. Increased sensitivity to cholinergic agents has also been observed in several human populations, including individuals suffering from depressive disorders, asthma, and chronic fatigue, conditions that share some symptoms with individuals suffering from chemical intolerance. Indeed, the FSL rats exhibit certain behavioral characteristics such as abnormal sleep, activity, and appetite that are similar to those reported in these human populations. In addition, the FSL rats have been reported to exhibit increased sensitivity to a variety of other chemical agents than cholinergic drugs. Peripheral tissues, such as intestinal and airway smooth muscle, appear to be more sensitive to both cholinergic agonists and an antigen, ovalbumin. Hypothermia, a centrally mediated response, is more pronounced in the FSL rats after nicotine and alcohol, as well as agents that are selective for the dopaminergic or serotonergic systems. However, there are differences in nicotinic but not dopamine receptors. Therefore, there may multiple mechanisms underlying the multiple chemical sensitivity/chemical intolerance of the FSL rats. An elucidation of these mechanisms may provide useful clues to those involved in chemical intolerance in humans.

Episodic exposures to chemicals: What relevance to chemical intolerance?

R.C. MacPhail, Neurotoxicology Division, National Health and Environmental Effects Research Laboratory, U.S. EPA, Research Triangle Park, NC.

Episodic exposures refer to intermittent acute exposures to chemicals that ordinarily have a rapid onset and short duration of effect. There have been a long tradition in pre-clinical behavioral pharmacology of using episodic-exposure paradigms in order to establish dose-response functions in individual organisms. In these experiments, stable baselines of behavior are first established, and then followed by administering varying doses of a drug intermittently, for example once or twice a week. The power of this approach is well-established; the within-subjects design reduces error variance, allows exploration of the entire range of effective doses, and can be used to identify individual differences in drug sensitivity. Of course, the approach is only applicable to reversibly acting compounds, and checks need to be included to insure effects of one dose are not influenced by prior exposure to another dose. We have used baseline approaches to evaluate the effects of pesticides and solvents on the behavior of adult male rats and mice. Moreover, a novel probabilistic dose-tolerance analysis applied to the data suggests substantial individual differences in chemical sensitivity, often spanning orders of magnitude. Further, more recent research has found systematic quantitative and qualitative changes in the behavioral effects of nicotine in rats when nicotine was given episodically at weekly intervals. The implications of these findings for understanding the etiology and dimensions of chemical intolerance will be the focus of further discussion.

ENVIRONMENTAL RISKS AND PUBLIC HEALTH Bernard D. Goldstein, M.D., Environmental and Occupational Health Sciences Institute (EOHSI), Piscataway, NJ. EOHSI is a joint program of UMDNJ-Robert Wood Johnson Medical School and Rutgers-The State University of New Jersey.

Environmental risks impact on public health through the action of chemical and physical agents and of lifestyle factors known to produce adverse health impacts, and through such processes as alteration of climate and of our biosphere that indirectly affect human health. Study of cause and effect relationships due to environmental factors usually focuses on known disease endpoints. But, the various definitions of health by national and international agencies all have in common the statement that health is not merely the absence of disease. Health involves the complete physical, mental and social well being of an individual. Taking this definition seriously requires us to conclude that the many individuals in our society who are symptomatic without any identifiable underlying disease are not healthy. It further requires that we consider appropriate public health approaches to respond to the health needs of these individuals. Good public health practice begins with surveillance, but effective surveillance requires a clear case definition, something often lacking when considering individuals with unexplained symptoms. An effective public health response requires research exploring potential pathways for the observed response, pathways that may be exploited for prevention and control.

CEREBRAL REPRESENTATION OF PAIN AND ITS MODULATION BY COGNITIVE INTERVENTIONS: POTENTIAL IMPLICATIONS FOR PATHOLOGICAL PAIN

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The investigation of brain activity using functional brain imaging techniques has provided new insights on the cerebral correlates of pain in humans. In accord with anatomical, electrophysiological, and lesion studies in animal and humans, a variety of nociceptive stimuli activate a widely distributed network of cerebral structures, including the thalamus and the somatosensory, insular, and anterior cingulate cortices. Abnormal activity within some of these regions has been associated with spontaneous pain and abnormal pain responses in clinical populations. In normal individuals activity within this network is correlated with subjective pain perception, has been associated with emotions, and is highly modifiable by cognitive interventions. The hypnotic modulation of pain unpleasantness is accompanied by changes in cingulate activity while the modulation of pain sensation intensity by hypnosis or attention produces changes mainly in somatosensory cortices. Furthermore, hypnotic analgesia influences both pain-related autonomic responses and spinally mediated nociceptive reflexes, suggesting the engagement of descending modulatory mechanisms. Other cognitive mediators such as expectations can produce robust changes in pain perception (e.g. in placebo analgesia). Some of these effects can be somatotopically specific, are at least partly dissociated from conditioning mechanisms, and likely depend on the activity in higher-order cerebral structures. The multiplicity and versatility of the neuro-cognitive mechanisms involved in pain modulation is suggestive of a determinant influence on clinical pain. We speculate that these mechanisms may further attenuate or promote central mechanisms involved in the transition from acute to pathological persistent pain states.

CENTRAL NEUROPLASTICITY AND PATHOLOGICAL PAIN.

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The traditional specificity theory of pain perception holds that pain involves a direct transmission system from somatic receptors to the brain. The amount of pain perceived, moreover, is assumed to be directly proportional to the extent of injury. Recent research, however, indicates far more complex mechanisms. Clinical and experimental evidence shows that noxious stimuli may sensitize central neural structures involved in pain perception. Salient clinical examples of these effects include amputees with pains in a phantom limb that are similar or identical to those felt in the limb before it was amputated, and patients after surgery who have benefited from pre-emptive analgesia which blocks the surgery-induced afferent barrage and/or its central consequences. Experimental evidence of these changes is illustrated by the development of sensitization, wind-up or expansion of receptive fields of CNS neurons, as well as by the enhancement of flexion reflexes and the persistence of pain or hyperalgesia after inputs from injured tissues are blocked. It is clear from the material presented that the perception of pain does not simply involve a moment-to-moment analysis of afferent noxious input, but rather, involves a dynamic process which is influenced by the effects of past experiences. Sensory stimuli act on neural systems which have been modified by past inputs, and the behavioural output is significantly influenced by the 'memory' of these prior events. An increased understanding of the central changes induced by peripheral injury or noxious stimulation should lead to new and improved clinical treatment for the relief and prevention of pathological pain.

Spinal Cord Neuroplasticity after Repeated Opioid Exposure and Nerve Injury **Jianren Mao, M.D., Ph.D., MGH Pain Center, Massachusetts General Hospital,** **Harvard Medical School, 15 Parkman Street, Boston, MA 02114**

Compelling evidence has accumulated indicating that neuroplastic changes occur within the central nervous system following repeated exposure to opioids. Such neuroplastic changes involve activation of N-methyl-D-aspartate (NMDA) receptors and subsequent intracellular cascades including protein kinase C translocation and activation. These cellular and intracellular changes have been implicated in the development of tolerance to the analgesic effects of morphine. Similar neuroplastic changes have been associated with the development of hyperalgesia resulting from peripheral nerve injury. A site of action involved in both hyperalgesia and opioid tolerance is likely to be in the superficial laminae of the spinal cord dorsal horn. Importantly, degenerative changes of spinal cord dorsal horn neurons, a potentially irreversible neurotoxic process, also occur following repeated exposure to opioids and peripheral nerve injury. These observations suggest that hyperalgesia and morphine tolerance may be interrelated through common neural substrates that interact at the level of NMDA receptor activation and related intracellular events. A better understanding of such interactions may provide a scientific basis for improved pain management with opioid analgesics.

CYTOKINES AND CHRONIC FATIGUE SYNDROME

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Patients with chronic fatigue syndrome (CFS) have predominantly two changes in immune function: [1] immune activation, as demonstrated by increased proportions of activated T lymphocytes and elevated levels of circulating cytokines, particularly T helper type 2 cytokines; and [2] poor cell-mediated immunity, with low natural killer cell cytotoxicity, poor lymphocyte response to mitogens in culture, and frequent immunoglobulin deficiencies, most often IgG1 and IgG3. The immune dysfunction in CFS shows a waxing and waning temporal pattern that could be either cause or effect of the physiological function derangements and/or activation of latent viruses or other pathogens seen in CFS. The interplay of the latter factors may also account for the perpetuation of disease and underlie the remission/exacerbation cycles characteristic of the disease. Therapeutic intervention aimed at induction of a more favorable T helper type 1 cytokine expression predominance has shown promise. Further basic science and clinical studies will help elucidate the role of each cytokine in CFS nosology.

MEDIATORS OF INFLAMMATION AND THEIR EFFECTS ON HUMAN SLEEP.

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The association between sleep, sleepiness and febrile illness has been recognized throughout medical history, yet little is known about the functional or adaptive role of sleep in host protection or in recovery processes. However, there is considerable evidence that cytokines and particularly the pro-inflammatory cytokine TNF- α and its soluble receptor P55 are involved in the regulation of sleep. In an *in vivo* human experimental endotoxin model, modest elevations (subpyrogenic levels) of TNF- α are associated with increased NREM sleep and delta power whereas strong elevations accompanied by fever disrupt sleep. Similarly in humans, the atypical immunomodulatory antipsychotic medication clozapine, increases the circulating levels of TNF- α and its soluble receptors and causes increased sleepiness and NREM sleep; whereas during clozapine induced fever, a known side effect in early stages of treatment, these cytokine levels are further increased and nocturnal sleep is disrupted. Therefore, cytokines such as TNF- α and its soluble receptors, present in the periphery and the CNS, comprise a link between peripheral immunostimulation and CNS-mediated behaviors such as sleep and sleepiness.

THE ROLE OF CYTOKINES IN PHYSIOLOGICAL SLEEP REGULATION James M. Krueger Washington State University, Pullman, WA

Several growth factors (GFs) are implicated in sleep regulation. It is posited that these GFs are produced in response to neural activity and affect input-output relationships within the neural circuits where they are produced, thereby inducing a local state shift. These GFs also influence synaptic efficacy. All the GFs currently identified as sleep regulatory substances are also implicated in synaptic plasticity. Among these substances, the most extensively studied for their role in sleep regulation are interleukin-1 β (IL-1) and tumor necrosis factor α (TNF). Injection of IL-1 or TNF enhances non-rapid eye movement sleep (NREMS). Inhibition of either IL-1 or TNF inhibits spontaneous sleep and the sleep rebound that occurs after sleep deprivation. Stimulation of the endogenous production of IL-1 and TNF enhances NREMS. Brain levels of IL-1 and TNF correlate with sleep propensity, e.g., after sleep deprivation their levels increase. IL-1 and TNF are part of a complex biochemical cascade regulating sleep. Downstream events include nitric oxide, growth hormone releasing hormone, nerve growth factor, nuclear factor kappa B and possibly adenosine and prostaglandins. Endogenous substances moderating the effects of IL-1 and TNF include anti-inflammatory cytokines such as IL-4, IL-10, and IL-13. Clinical conditions altering IL-1 or TNF activity are associated with changes in sleep, e.g., infectious disease and sleep apnea. As our knowledge of the biochemical regulation of sleep progresses our understanding of sleep function and of many clinical conditions will improve. Supported by NS 25378 and NS31453.

CYTOKINES AND SICKNESS BEHAVIOR

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The behavioral alterations that develop in sick individuals during the course of an episode of sickness due to infection and inflammation include depressed activity, decreased exploration, reduced social interactions, decreased food and water intake, and disappearance of body care activities. These behavioral alterations are referred to as sickness behavior. The mechanisms of sickness behavior have been studied at several levels of investigation. At the whole organism level, sickness behavior is the expression of a central motivational state that reorganizes the organism's priorities to cope with the particular threat represented by pathogenic microorganisms. This motivational aspect of sickness behavior is important since it implies that sickness can be conditioned to environmental stimuli. At the molecular level, sickness behavior is triggered by the release of proinflammatory cytokines by activated monocytes and macrophages. Peripherally released cytokines induce the synthesis of cytokines in circumventricular organs and choroid plexus, which diffuse from there into the brain parenchyma. The development of sickness behavior is dependent on these centrally produced cytokines, as demonstrated by pharmacological experiments using centrally administered antagonists of cytokine actions. Brain interleukin-1 is one of the most important cytokines for the development of sickness behavior. Sickness behavior is normally a transient response, which dissipates over time. In terms of mechanisms, this dissipation is not passive. It involves a number of endogenous regulatory factors that oppose the production and effects of cytokines. These molecules have been termed cryogens, by analogy with pyrogens. Already identified cryogens include glucocorticoids, vasopressin and anti-inflammatory cytokines. The existence of a brain cytokine compartment that is normally triggered by infectious agents and mediates the development of sickness behavior has important psychopathological implications, as shown by the converging clinical and experimental evidence in favor of a relationship between cytokines and depression.

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ROLE OF GASEOUS NEUROTRANSMITTERS IN THE HPA AXIS

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Nitric oxide (NO) and carbon monoxide (CO) have recently been shown to participate in the response of the hypothalamic-pituitary-adrenal (HPA) axis response to homeostatic challenges. We reported that the influence exerted by these gases appears to depend on the type of stimulus to which the HPA axis is exposed. Following systemic administration of pro-inflammatory cytokines such as tumor necrosis factor- α , interleukin (IL)-1 β or IL-6, or during inflammatory processes that involves the release of these proteins in the general circulation, ACTH secretion is enhanced by compounds that block NO formation [such as N ω -nitro-L-arginine-methylester (L-NAME)], but not by metalloporphyrins that block CO synthesis. While these immune stimuli increase plasma ACTH levels via mechanisms that depend on the release of corticotropin-releasing factor (CRF) and vasopressin (VP) from nerve terminals, only the effect of VP is augmented by L-NAME. These results indicate that NO, but not CO, restrain the pituitary response to VP and might also inhibit events taking place within the median eminence. The situation is different during exposure to neurogenic stimuli, conditions under which NO and CO act both alone and in conjunction with each other to augment the activity of neurons expressing CRF and VP neurons in the paraventricular nucleus (PVN) of the hypothalamus. Consequently, the net ACTH response to stimuli that involve not only CRF/VP release from nerve terminals but also the acute activation of the PVN, depends on the balance between the opposite influence of NO within the two sites.

Plasticity of the hippocampus: adaptation to chronic stress and allostatic load

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The hippocampus is an important structure for declarative, spatial and contextual memory and the perception of chronic pain. It is vulnerable to damage from seizures, ischemia and head trauma, and it is particularly sensitive to the effects of adrenal glucocorticoids secreted during the diurnal rhythm and chronic stress. Adrenal steroids typically have adaptive effects in the short-run but promote pathophysiology when there is either repeated stress or dysregulation of the HPA axis. The damaging actions of glucocorticoids under such conditions have been termed "allostatic load" (McEwen, B.S. Protective and damaging effects of stress mediators. *New England J. Med.* 338: 171-179 (1998)). Adrenal steroids display both protective and damaging effects in the hippocampus. They biphasically modulate excitability of hippocampal neurons and contextual and declarative memory in a reversible manner. The hippocampus also displays structural plasticity, involving ongoing neurogenesis of the dentate gyrus, synaptogenesis under control of estrogens in the CA1 region, and dendritic remodeling caused by repeated stress or elevated levels of exogenous glucocorticoids in the CA3 region. In all 3 forms of structural plasticity, excitatory amino acids participate along with circulating steroid hormones. Glucocorticoids and stressors suppress neurogenesis in the dentate gyrus. They also potentiate the damage produced by ischemia and seizures. Moreover, the aging rat hippocampus displays elevated and prolonged levels excitatory amino acids released during acute stress, a form of allostatic load. Our working hypothesis is that hippocampal structural plasticity in response to repeated stress begins as an adaptive and protective response, but ends up as damage if the imbalance in the regulation of the key mediators is not resolved. This will be illustrated by describing the behavioral and neural consequences of repeated restraint stress in rats and comparing this will hippocampal structural plasticity during psychosocial stress and hibernation, and with changes that occur in hippocampal volume and morphology in recurrent depressive illness.

CONDITIONING OF SOMATIC COMPLAINTS IN HUMANS : EXPERIMENTS WITH ODORS

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Pavlovian conditioning has been suggested as a potential explanation for MCS. However, evidence mostly relied on case reports and anecdotal evidence. In order to experimentally test assumptions implied in this account, we developed a respiratory learning paradigm with odors as conditioned stimuli (CSs) and 7.4 % CO₂ enriched air as the unconditioned stimulus (US), presented as compounds during 2 min. breathing trials. In a review of results, we show that 1. subjects learn to exhibit respiratory responses and somatic symptoms upon presenting the odors only; 2. this effect is facilitated by negative affective valence of the odors; 3. symptoms learned to one odor automatically generalize to new odors; 4. symptoms are better learned by normal subjects scoring high on neuroticism and by psychosomatic patients and 5. learned symptoms can be eliminated in a typical Pavlovian extinction paradigm. In addition, it was shown that conscious awareness of the contingencies between odors and CO₂ inhalation is not sufficient to explain the effects. Using mental imagery scripts to replace odors as CSs in a similar paradigm, it was shown that also thoughts and images may come to serve as CS-triggers for symptoms, provided that they are stressful. These data strongly support the plausibility of a Pavlovian condition hypothesis for MCS. Implications for treatment and unresolved questions within this view will be discussed.

PAVLOVIAN CONDITIONING OF EMOTIONAL RESPONSES TO OLFACTORY AND CONTEXTUAL STIMULI: A POTENTIAL MODEL FOR THE DEVELOPMENT AND EXPRESSION OF CHEMICAL INTOLERANCE? Tim Otto, Ph.D. and Nicholas

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Chemical intolerance (CI) in humans is a poorly understood phenomenon of uncertain etiology, seemingly influenced by multiple of factors both within and between affected individuals. Several authors have suggested that the development of CI in some individuals may be due, at least in part, to Pavlovian conditioning processes in which the expression of overt symptoms to certain substances reflect classically conditioned responses to previously neutral olfactory and contextual stimuli. In this paper, we will focus mainly on recent studies examining olfactory and contextual conditioning in experimental animals. Furthermore, as significant advances have been made in delineating the brain areas that underlie these learned responses, we also review recent research on the contributions of the amygdala and perirhinal cortical region to these types of conditioning. These empirical data are discussed in light of their potential relationship to the development and expression of CI.

A Priority Queue Model of the Gate Control theory of Pain

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While the Gate Control theory of Pain (1) was a landmark in our understanding of pain modulation, so far, no mathematical formulation has been available for it. We discuss pain modulation as a 'priority queue' problem. The mathematical theory of Queueing systems deals with probabilistic models of systems where 'service' is required by a 'customer' and a 'queue' ensues if the 'server' is not immediately available for service for whatever reason. Our previous papers have dealt with the application of this theory to various physiological problems including those relating to the lower urinary tract, the cardiovascular system, and clinical toxicology (2). In the operations research literature, gates (physical that is) have been modeled as queueing problems. In our model, afferent pain impulses ('customers') from the periphery encounter a bottleneck at the substantia gelatinosa ('server') and find themselves competing with impulses from the skin and elsewhere (other 'customers') to make their way to the higher centres. The two important variables in this model are traffic intensity and queue priority. Queue priority and hence transmissivity is subject to modulation. It is demonstrated how a high traffic intensity and/or high priority of other impulses at the substantia gelatinosa can result in an almost complete blockage of transmission of pain impulses to the higher centers. This model places the classical Gate Control theory of Pain modulation on a firm mathematical foundation. Moreover, it paves the way for the formulation of a unified theory of pain based on the theory of complex adaptive systems by including the more recent concepts of neuronal plasticity.

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CENTRAL NERVOUS SYSTEM EFFECTS FROM A PERIPHERALLY ACTING CHOLINESTERASE INHIBITING AGENT: INTERACTION WITH STRESS OR GENETICS.

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Many pharmacological agents have been developed to act solely upon the peripheral nervous system. One such agent, pyridostigmine bromide (PSB), was developed to inhibit peripheral cholinesterase activity (at the neuromuscular junction), as a treatment for myasthenia gravis and, more recently, as a preventative pretreatment to the ill-effects of nerve-gas exposure. However, the patient populations studied in the past had either cholinergic deficiencies or were not "challenged" in any manner that would elicit a stress response. Recent reports have implicated PSB as a centrally acting agent when it is combined with a regimen of stress. Our research has been focused on evaluating this hypothesis both behaviorally and physiologically. By manipulating the length of treatment and co-presentation of stress, our behavioral and physiological results support the hypothesis that PSB can influence central nervous system activity under certain conditions. Increased post-treatment startle was evident only in the WKY strain of rat. Brain acetylcholinesterase activity was affected when PSB treatment followed stress (regardless of rat strain). These findings illustrate that environmental conditions and genetics should be considered as potential confounding factors in models of persistent physiological and behavioral consequences of chemical agents. These studies were supported by the Center for Environmental Hazards Research and DVA Medical Research funding to RJS.

Generalization of learned symptoms as a possible mechanism in MCS

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Major research issues were whether symptoms acquired in a Pavlovian learning paradigm in response to odors can generalize to new odors and whether the generalization is modulated by the delay between acquisition and test. Diluted ammonia and niaouli were used as conditional odor stimuli (CSs). One odor was mixed with 7.5 % CO₂-enriched air (unconditional stimulus) during 2 min breathing trials (CS+ trial), while the other odor was presented with air (CS- trial). Three CS+ and three CS- trials occurred in a semi-randomized order (acquisition phase). The test phase implied the presentation of one CS+ Only (CS+ without CO₂) and one CS- test trial, followed by three trials using new odors (butyric acid, acetic acid, and citric aroma). Half of the subjects (n=28) were tested immediately, the other half were tested after one week. Ventilatory responses were measured during and somatic symptoms after each trial. Results showed that more symptoms were reported upon confrontation with the CS+ odor alone, but only when ammonia was used as CS+. In those subjects showing clear conditioning effects, more symptoms were also reported to butyric acid and acetic acid, showing generalization of learned symptoms. The delay between acquisition and test had no effect. Negative Affectivity (NA) of the subjects modulated both the learning and the generalization of symptoms: the effects were manifest only in high NA participants. These findings further support our conditioning model for Multiple Chemical Sensitivity.

Failure to replicate learning of symptoms in response to odors in a single odor respiratory conditioning paradigm

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In previous experiments, we showed that subjects acquired symptoms in response to harmless odors (conditioned stimuli, CS), if these had been mixed previously with a physiological challenge (CO₂ inhalation) that originally had caused these symptoms (unconditioned stimulus, US). The results provided strong evidence in support of a Pavlovian conditioning hypothesis of MCS. These studies used a differential conditioning paradigm: one of two odors was paired with CO₂ whereas a control odor was inhaled with regular air. As a result, the conditioning effect was tested within subjects and within odor. In the present set of studies, we used a non-differential conditioning paradigm in order to improve the ecological validity of our approach: only one odor was used and associated with CO₂ inhalation and the conditioning effect was tested between subjects. Three experiments were run using four CS-US pairings in the experimental condition. Experiment 1 (n=50) used diluted ammonia as CS, 7.5% CO₂ as the US and several control conditions ('random', explicitly unpaired, CS-only, US-only). In experiment 2 (n = 48), we increased the intensity of the US to 10 % CO₂. In experiment 3 (n = 40), the CS was ammonia in one group and niaouli in another group. Contrary to our earlier findings, none of these experiments showed elevated symptoms upon presenting the odor only. The reliable presence of learning effects in a differential paradigm and their reliable absence in a non-differential paradigm suggests that perceptual-cognitive mechanisms determining the salience of odors play an important role in symptom learning in response to odors.

Limbic Hypermetabolism in Patients with Chemical Intolerance. Human PET Studies

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Neurotoxic injury is known to effect memory and cognitive functions, coordination and balance, and also behavior. In addition, patients may develop sensitivity to chemicals. Their reactions to chemicals may range from increased irritability to emotional instability with "irrational" behavior including panic attacks. Bell, Sorg, and others have suggested and discussed limbic system involvement with kindling as a possible mechanism for the above reactions.

We studied seven adult patients who had developed the above clinical syndrome. All had been exposed to solvents, pesticides or other known neurotoxic compounds and exhibited significant chronic symptoms (incl. chemical intolerance) and signs which continued for months after exposure.

PET scans in the above patients were compared with a control group and showed significant hypometabolism in many cortical areas. By contrast, significant hypermetabolism was found in the extended amygdala region and adjacent structures. Since hypermetabolism can represent seizure activity and amygdaloid seizures can represent as panic attacks, and since the amygdala is one of the most easily kindled structures of the brain, our preliminary data supports the concept of limbic system involvement and kindling in patients with neurotoxic injury and resulting chemical intolerance.

Elevated Nitric Oxide/Peroxynitrite Mechanism for the Common Etiology of Multiple Chemical Sensitivity (MCS), Chronic Fatigue Syndrome (CFS) and Posttraumatic Stress Disorder (PTSD). Martin L. Pall* and James D. Satterlee**, School of Molecular Biosciences* and Department of Chemistry**, Wahington State University, Pullman, WA 99164.

We have proposed a vicious cycle mechanism for CFS in which elevated levels of peroxynitrite and its two precursors, nitric oxide and superoxide, is induced by infection or other stresses and is maintained by six different positive feedback loops, producing a sustained elevation of the levels of these three compounds, leading to chronic pathology. CFS, MCS and PTSD show considerable overlap, in their symptoms, their occurrence in individual patients and their inducers, suggesting a similar etiology. We propose, therefore that they share the same biochemical mechanism, albeit with somewhat different tissue distribution. Evidence is reviewed that organic solvents and pesticides that induce MCS can induce nitric oxide. Other evidence for the proposed mechanism of MCS in humans include elevated oxidative stress, elevated levels of inflammatory cytokines, and elevated levels of neopterin (a biochemical marker for nitric oxide synthase (NOS) induction). Studies of animal models of MCS have shown that nitric oxide elevation is required for induction of the characteristic sensitization or kindling response, based on studies using NOS inhibitors and a mouse disrupted in the nNOS gene. A similar pattern of evidence in PTSD supports a role for nitric oxide/peroxynitrite. In summary, multiple observations provide support for the patterns predicted by the elevated nitric oxide/peroxynitrite mechanism of CFS, MCS and PTSD, providing a cogent explanation for the overlaps seen among these three diseases. Supported by the AFOSR.

The Role of Neural Plasticity in Chemical Intolerance

A New York Academy of Sciences Conference

Conclusions

Chemical Intolerance (CI) in humans may represent the culmination of concurrent processes that depend upon the susceptibility to induction of neural plasticity in one or more neural pathways. The constellation of symptoms may vary among individuals due to the specific pathways influenced by genetic factors and environmental stimuli.

The conference addressed issues critical to the hypothesis that neural plasticity plays an important role in the development of CI, regardless of whether CI represents a phenomenon of "psychogenic" or "biogenic" origin. While this topic has been discussed at previous conferences which focus on CI, the presentations regarding mechanistic studies have often been restricted to a single session, and only one meeting in the past four years (held by the U.S. Environmental Protection Agency) has focused on pre-clinical studies (animal models) of CI. In contrast, the present conference sought to bind together the session topics via a common process of neural plasticity that likely underlies conditioning to stimuli, enhanced pain, stress effects and neurally-mediated inflammatory responses, all of which appear to be important contributing factors in CI. By emphasizing this common factor it is expected that animal systems that model specific aspects of CI may be developed by experts in their respective fields. The development of animal models are necessary for understanding the mechanisms which underlie altered sensitivity to chemicals, and represent a rational approach for rigorous dialogue and consensus regarding treatment strategies.

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